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Complications and outcome of assisted reproduction technologies in overweight and obese women[†]

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BACKGROUND: Based on a presumed negative impact of overweight and obesity on reproductive capacity and pregnancy outcome, some national guidelines and clinicians have argued that there should be an upper limit for a woman's BMI to access assisted reproductive technologies (ART). However, evidence on the risk of complications or expected success rate of ART in obese women is scarce. We therefore performed a systematic review on the subject.

METHODS: We searched the literature for studies reporting on complications or success rates in overweight and obese women undergoing ART. Articles were scored on methodological quality. We calculated pooled odds ratios (ORs) to express the association between overweight and obesity on the one hand, and complications and success rates of ART on the other hand. We only pooled results if data were available per woman instead of per cycle or embryo transfer.

RESULTS: We detected 14 studies that reported on the association between overweight and complications during or after ART, of which 6 reported on ovarian hyperstimulation syndrome (OHSS), 7 on multiple pregnancies and 6 on ectopic pregnancies. None of the individual studies found a positive association between overweight and ART complications. The pooled ORs for overweight versus normal weight for OHSS, multiple pregnancy and ectopic pregnancy were 1.0 [95% confidence interval (CI) 0.77–1.3], 0.97 (95% CI 0.91–1.04) and 0.96 (95% CI 0.54–1.7), respectively. In 27 studies that reported on BMI and the success of ART, the pooled ORs for overweight versus normal weight on live birth, ongoing and clinical pregnancy following ART were OR 0.90 (95% CI 0.82–1.0), 1.01 (95% CI 0.75–1.4) and OR 0.94 (95% CI 0.69–1.3), respectively.

CONCLUSIONS: Data on complications following ART are scarce and therefore a registration system should be implemented in order to gain more insight into this subject. In the available literature, there is no evidence of overweight or obesity increasing the risk of complications following ART. Furthermore, they only marginally reduce the success rates. Based on the currently available data, overweight and obesity in itself should not be a reason to withhold ART.

Key words: assisted reproduction / body mass / ectopic pregnancy / OHSS / multiple pregnancy

Introduction

Obesity is a growing problem throughout the Western world with more than half of the women in the UK and USA being overweight or obese, and up to 25% of women in their reproductive age being obese (Haslam and James, 2005; Balen and Anderson, 2007). Several studies have shown that obesity is associated with a reduced fecundity (Jensen *et al.*, 1999; Ramlau-Hansen *et al.*,

2007; Van der Steeg *et al.*, 2007). In addition, obese women are more prone to anovulation (Pasquali *et al.*, 2007) and symptoms of polycystic ovarian syndrome (PCOS) are aggravated by obesity. Pregnancy in overweight and obese women is associated with an increased risk of complications, leading to higher maternal and neonatal morbidity and mortality and increased costs (Sebire *et al.*, 2001; Cedergren, 2004; Linné, 2004; Weiss *et al.*, 2004; Usha Kiran *et al.*, 2005).

[†]Presented at the 26th Annual Meeting of ESHRE, Rome, Italy.

Due to the worldwide epidemic of obesity, an increasing proportion of women seeking medical help for subfertility will be overweight or obese. In their analysis, Vahratian and Smith (2009) found that, in comparison to normal weight women, obese women seek medical attention for their subfertility more often. They receive, however, the least fertility-related services. Guidelines that regulate access to fertility care for overweight and obese women vary worldwide. In New Zealand, for example, women with a BMI of $>32 \text{ kg/m}^2$ are excluded from any fertility treatment. Almost all clinics in the UK have an upper BMI limit for access to assisted reproductive technologies (ART), ranging from 25 to 40 kg/m^2 (Gillett et al., 2006; Zachariah et al., 2006; Awartani et al., 2009). The UK national guideline recommends that women with a BMI above 29 kg/m^2 should be informed about their lower pregnancy chances but does not explicitly prescribe a BMI cut-off point for treatment (NICE, 2004).

Recently, the ESHRE Task Force on Ethics and Law (2010), reported on lifestyle-related factors, i.e. alcohol consumption, smoking and obesity, and access to medically assisted reproduction. It was argued that if a high risk of serious harm for the future child is anticipated, fertility treatment should be denied. Although this risk is obvious for alcohol consumption and smoking, it is unclear whether this recommendation can be applied in daily clinical practice with respect to adipose subfertile women.

Data regarding the impact of overweight and obesity on fertility treatment outcome are conflicting, with some studies showing a negative impact on pregnancy rates, whereas others report no impact (Fedorcsak et al., 2004; Balen et al., 2006; Dokras et al., 2006). In a systematic review of the literature on overweight and ART, Maheshwari et al. (2007) concluded that there is insufficient evidence of the effect of BMI on the outcome of ART to justify denial of treatment for overweight and obese women.

Apart from the impact of overweight and obesity on spontaneous pregnancy rates and the course of pregnancy, little is known about the impact of BMI on complications of ART. Some have suggested that women with a high BMI are more prone to complications during their fertility treatment and fertility treatment should therefore be denied.

The aim of the present systematic review was to investigate the association between overweight or obesity and the occurrence of complications of ART, as well as the expected outcome in terms of clinical and ongoing pregnancy and live birth rates. To do so, we updated the review of Maheshwari et al. (2007), and added a new review with data on the impact of overweight and obesity on the risk of complications of ART.

Materials and Methods

We searched the literature from January 1999 till July 2011 for studies that reported on the association between overweight and obesity on complications of ART, as well as for studies that reported on the association between overweight and obesity and the effectiveness of ART. We searched PubMed, Embase, DARE and the Cochrane Library for studies reporting on the association between BMI and complications of ART. Only studies in English were included. To do so, we combined the keywords ('obesity', 'overweight' or 'body mass index'), ('complication', 'ovarian hyperstimulation syndrome', 'ectopic pregnancy', 'multiple pregnancy', 'infection', 'haemorrhage' or 'injury') and ('*in vitro* fertilisation').

In the search for studies on the association between overweight and obesity and the outcome of ART, we added the keywords ('outcome', 'pregnancy rate', 'live birth rate'). Additionally, we checked the references of the selected articles for relevant articles.

Since overweight and obese women are more prone to PCOS, which has an increased risk of ovarian hyperstimulation syndrome (OHSS) after ART (Tummon et al., 2005), we searched and described this group separately using keywords mentioned above in combination with ('polycystic ovarian syndrome').

Study quality

Two reviewers independently screened titles and abstracts of all retrieved studies (A.M.H.K. and M.A.Q.M.). We obtained full-text reports of studies that were likely to evaluate the association between BMI and complications or BMI and success rates of ART. If the title did not contain any of our keywords, it was excluded. Reviews were excluded. If not enough data were available for a 2×2 table, studies were excluded. Studies reporting on fertility treatment other than IVF/ICSI were excluded. Studies that did not report sufficient data for a 2×2 table, but for which data could possibly be obtained from the authors, were also evaluated.

We extracted data on study characteristics, study quality and 2×2 tables of test accuracy using a predesigned data extraction form. In the case of multiple publications on the same data set, we used all publications to acquire complete data. The most recent and complete results were included in the analysis. If data on test accuracy or on other relevant characteristics were missing, we contacted the corresponding author. Disagreement on data was resolved by discussion and consensus. If consensus could not be reached, a third reviewer (B.W.M.) was consulted.

Methodological quality of selected papers was evaluated using QUADAS, a tool for quality assessment of studies of diagnostic accuracy (Whiting et al., 2003). We adjusted the original QUADAS list in order to evaluate items that we considered of specific importance for this systematic review. Included studies were evaluated on 15 items concerning patient selection, verification, description of the tests and of the study population. A comprehensive list of items on which the methodological study quality was assessed is available from the authors on request.

We defined complications of ART as OHSS, multiple pregnancy, ectopic pregnancy, haemorrhage, infection or injury to pelvic structures. We defined success rates of ART as clinical pregnancy rate, ongoing pregnancy rate, live birth rate and delivery rate.

If data on live birth rates were available, we used these data to calculate odds ratios (ORs) with 95% confidence intervals (CIs). If live birth rates were not available, we used pregnancy rates (clinical or ongoing pregnancy) for the calculations. Some studies report outcome per cycle, with several cycles per woman included. This would suggest better results in terms of pregnancy rates. Therefore, we report outcome (per first cycle) per woman where possible. In order to obtain clinically useful outcome, we chose to only pool data if results per woman were available.

Data synthesis

From each article, we calculated the OR from a 2×2 table cross-classifying BMI and one of the aforementioned outcomes. We used the WHO definitions for overweight (BMI $> 25 \text{ kg/m}^2$) and obesity (BMI $> 30 \text{ kg/m}^2$), where possible. Data of each outcome were pooled if the data were analysed per woman and if there were at least two studies with similar definition of the outcome and similar range of BMI for the comparison groups. Combined ORs and 95% CI were calculated using the Review Manager (RevMan 5.1) computer software of the Cochrane Collaboration. The heterogeneity was assessed with the I^2 -statistic for

inconsistency. A value of $>50\%$ was considered as substantial heterogeneity (Higgins *et al.*, 2003). In the case of statistical homogeneity, we used a fixed-effect model. In the case of substantial heterogeneity, we used the random-effect model instead of the fixed-effect model.

Results

Our literature search resulted in 91 studies on the association between BMI and complications of ART and 242 studies on the association between BMI and the effectiveness of ART, respectively. The separate search on the association between overweight women with PCOS and complications after ART or the effectiveness of ART yielded a total of 77 articles in total.

Based on titles and abstracts derived from the search on studies between BMI and complications, 24 articles were identified as potentially eligible for the review (Fig. 1).

Eleven studies were excluded because they were solely concerned with women with PCOS and another 8 because they lacked adequate data; however, another 9 studies were identified by cross-referencing making 14 available for analysis.

Table 1 shows the characteristics of the 14 studies and the results per woman if available, otherwise per cycle for each complication. Only 2 out of the 14 studies were prospective. It was unclear whether a BMI threshold was used for access to ART. None of the

researchers reported blinding for BMI status in the assessment of end-points. Of the 14 studies, 6 reported on the relationship between OHSS and BMI, 7 reported on the relationship between multiple pregnancies and BMI and 6 reported on the relationship between ectopic pregnancies and BMI. We found no studies that reported on the complications infection, haemorrhage or injury to pelvic structures in relation to BMI in women undergoing ART. Three out of the 14 studies used a different definition than the WHO definition for overweight (Table 1 legend).

None of the six studies that reported on OHSS found a significant difference between the risk of OHSS in normal and overweight women. The pooled OR for overweight woman was 1.0 (95% CI 0.77–1.3) (Fig. 2).

Of the seven studies that reported on the relation between BMI and multiple pregnancies for women undergoing ART, the retrospective cohort study of Spandorfer *et al.* (2004) found a significantly higher risk of multiple pregnancies in women with normal weight following ART, whereas six other studies did not. The pooled OR expressing the association between overweight and the risk of multiple pregnancies was 0.97 (95% CI 0.91–1.04) (Fig. 3).

Six studies reported on the association between BMI and ectopic pregnancies. None of these studies revealed a significant difference between normal and overweight women. The pooled OR expressing the association between overweight and the risk of ectopic pregnancy was 0.96 (95% CI 0.54–1.7) (Fig. 4).

After screening of titles and abstracts derived from the search on 242 studies reporting on the association between BMI and the effectiveness of ART, 39 articles were identified as potentially eligible for the review. After exclusion of papers that studied only patients with PCOS and those with insufficient data, 25 papers remained and a further 2 were identified by cross-referencing yielding 27 suitable for analysis (Fig. 5).

Of the 27 included studies, 4 were prospective (Table II). Eleven studies reported on live birth rates, 2 on delivery rates, whereas 14 studies reported on pregnancy rates. The definition of delivery rate given in Dokras *et al.* (2006) is delivery after 20 weeks of gestation, whereas no definition is provided in Wittemer *et al.* (2000). Nine studies reported on clinical pregnancy rate, four on ongoing pregnancy rate and one reported on fecundity. Definitions of these outcome measures differed between studies. Six out of the 27 studies used a different definition for overweight and obesity than the WHO definition (Table II legend).

In 4 of the 27 included studies, a significant negative effect of an increased BMI on outcome was found, 22 studies did not find a significant association between BMI and ART outcome, and 1 study reported significantly more pregnancies in obese women. In 17 studies, results were presented per woman, and in 10 studies, results were presented per cycle or per embryo transfer (ET). Therefore, not all study results were comparable, and as a result, only seven studies could be pooled for the live birth rate per woman, our primary interest.

Overweight women undergoing ART had a significant lower live birth rate after ART than women with a normal weight [OR 0.90 (95% CI 0.82–1.0)] (Fig. 6), whereas obesity did not show a statistically significant difference in six studies including almost 10 000 women [OR 0.89 (95% CI 0.76–1.03)]. Clinical pregnancy rates were not different for overweight and normal weight women [OR 0.94 (95% CI

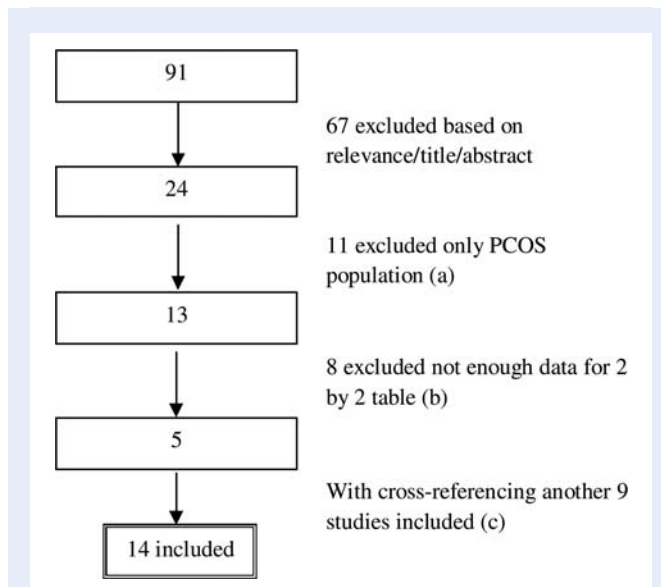


Figure 1 Flowchart in/exclusion studies for complications in ART. (a) Beydoun *et al.* (2009), Esinler *et al.* (2005), Fedorcsák *et al.* (2001), Kolibianakis *et al.* (2003), Kumbak and Kahraman (2009), Kurzawa *et al.* (2008), Li *et al.* (2010), Liberty *et al.* (2010), Lu *et al.* (2005), Salobir *et al.* (2002), Yarali *et al.* (2004). (b) Aramwit *et al.* (2008), Brannian *et al.* (2001), la Cour Freiesleben *et al.* (2011), Dechaud *et al.* (2006), Jacobsen *et al.* (2008), Jayaprakasan *et al.* (2009), Lee *et al.* (2008), Tur *et al.* (2001). (c) Dokras *et al.* (2006), Fedorcsák *et al.* (2004), Luke *et al.* (2011), Maheshwari (2009a), Matalliotakis *et al.* (2008), Sathya *et al.* (2010), Spandorfer *et al.* (2004), Van Swieten *et al.* (2005), Zhang *et al.* (2010).

Table I Incidence of complications following ART in overweight^a versus normal weight women.

Study	ART	n	Per	Complication rate in overweight ^a versus normal weight women								
				OHSS			Multiple pregnancy			Ectopic pregnancy		
				Incidence %		OR (95% CI)	Incidence % (p/p)		OR (95% CI)	Incidence % (p/p)		OR (95% CI)
				BMI > 25	BMI < 25		BMI > 25	BMI < 25		BMI > 25	BMI < 25	
Luke <i>et al.</i> (2011)	IVF	451 63	ET	NA	NA	NA	32	32	1.0 (0.9 to 1.1)	NA	NA	NA
Farhi <i>et al.</i> (2010)	IVF	233	Woman	2.7	3.8	0.7 (0.1 to 3.7)	NA	NA	NA	NA	NA	NA
Sathya <i>et al.</i> (2010)	IVF	308	Woman	NA	NA	NA	32	26	1.3 (0.6 to 3.1)	6.7	2.6	2.7 (0.3 to 22.7)
Zhang <i>et al.</i> (2010)	IVF/ICSI	2628	Woman	NA	NA	NA	NA	NA	NA	4.5	3.8	1.2 (0.5 to 2.9)
Maheshwari <i>et al.</i> (2009a)	IVF	1756	Woman	10.3	10.2	1.0 (0.7 to 1.4)	18	21	0.9 (0.6 to 1.3)	NA	NA	NA
Sneed <i>et al.</i> (2008)	IVF/ICSI	1273	Woman	NA	NA	NA	NA	NA	NA	1.7	3.0	0.6 (0.2 to 1.8)
Matalliotakis <i>et al.</i> (2008)	IVF/ICSI	278	Woman	NA	NA	NA	28 ^b	27 ^b	1.1 (0.5 to 2.1) ^b	1.1 ^b	1.2 ^b	1.0 (0.06 to 15.5) ^b
Esinler <i>et al.</i> (2008)	ICSI	775	ET	0.8	1.0	0.9 (0.2 to 3.0)	47	52	0.8 (0.6 to 1.2)	NA	NA	NA
Dokras <i>et al.</i> (2006)	IVF/ICSI	1291	Woman	4.8	4.8	1.0 (0.6 to 1.6)	28	31	0.9 (0.6 to 1.2)	NA	NA	NA
Van Swieten <i>et al.</i> (2005) ^c	IVF/ICSI	162	Woman	4.9	5.0	1.0 (0.2 to 4.3)	NA	NA	NA	NA	NA	NA
Spandorfer <i>et al.</i> (2004)	IVF/ICSI	828	Cycle	NA	NA	NA	36 ^d	52 ^d	0.5 (0.3 to 0.8) ^d	NA	NA	NA
Fedorcsak <i>et al.</i> (2004)	IVF/ICSI	2660	Woman	NA	NA	NA	NA	NA	NA	0.5	1.7	0.3 (0.03 to 2.0)
Wittemer <i>et al.</i> (2000)	IVF/ICSI	325	Cycle	NA	NA	NA	NA	NA	NA	15.0	5.0	3.4 (0.6 to 18.2)
Lashen <i>et al.</i> (1999) ^c	IVF	228	Woman	2.6 ^e	5.3 ^e	0.5 (0.1 to 2.4)	NA	NA	NA	NA	NA	NA

OHSS, ovarian hyperstimulation syndrome; p/p, per pregnancy; NA, not available.

^aComparisons as stated except where indicated ^bBMI > 24, ^dBMI > 27, ^eBMI > 28 versus BMI 20–25.^cProspective study, others were retrospective.

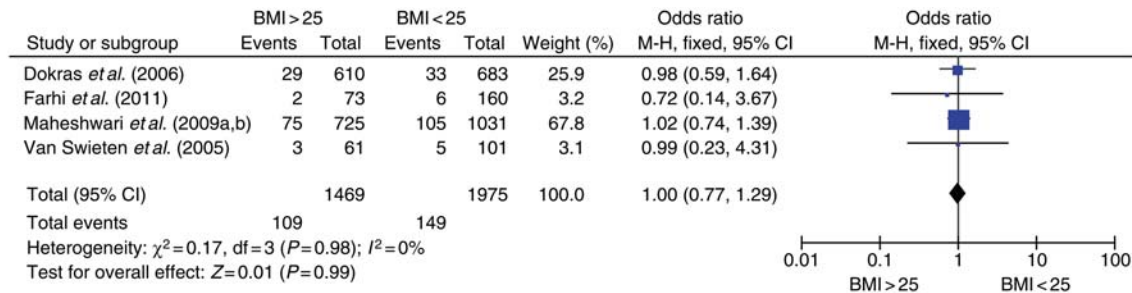


Figure 2 OHSS for overweight and normal weight women.

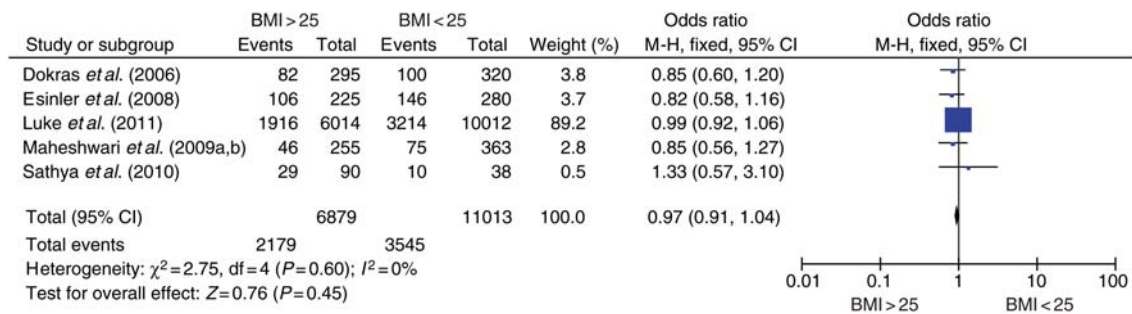


Figure 3 Multiple pregnancies for overweight and normal weight women.

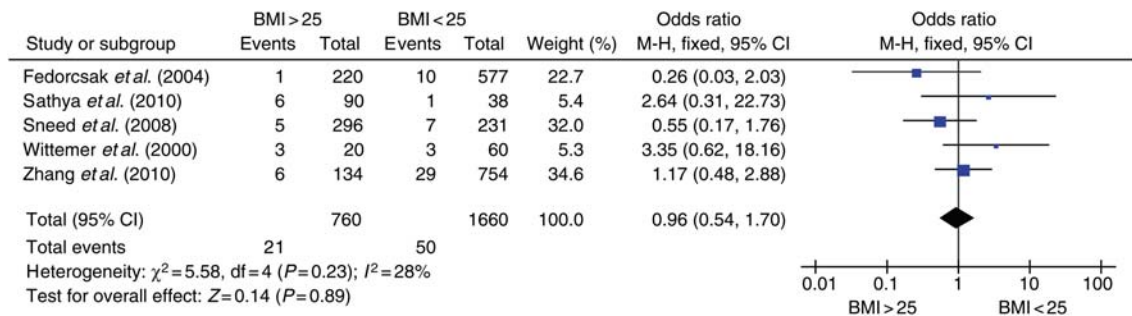


Figure 4 Ectopic pregnancies for overweight and normal weight women.

0.69–1.3)] or for obese women when compared with normal weight women [OR 0.97 (95% CI 0.59–1.6)]. For ongoing pregnancy rates, the pooled ORs were 1.01 (95% CI 0.75–1.4) and 0.96 (95% CI 0.64–1.4) for overweight and obesity, respectively (data not shown). Our search retrieved 77 studies on the association between overweight women with PCOS and the effectiveness of ART. Two studies report on complications in PCOS women with respect to their BMI. Ozgun *et al.* (2011) report on multiple pregnancy rate, showing no difference between BMI < 30 versus > 30 kg/m² ($P = 1$). Liberty *et al.* (2010) describe women with haemorrhage after oocyte retrieval, in which they conclude that lean women with

PCOS (BMI 19–21 kg/m²) are at more risk of this complication (4.5 versus 0%) than obese women with PCOS. Four studies reported on BMI and outcome in PCOS women (Table III). All studies showed better outcome for normal weight women, with an extreme OR 0.2 (95% CI 0.01–1.9) for live birth rates for overweight woman in McCormick *et al.* (2008).

Discussion

 In this systematic review, we assessed the association between overweight and obesity on the one hand and complications and success

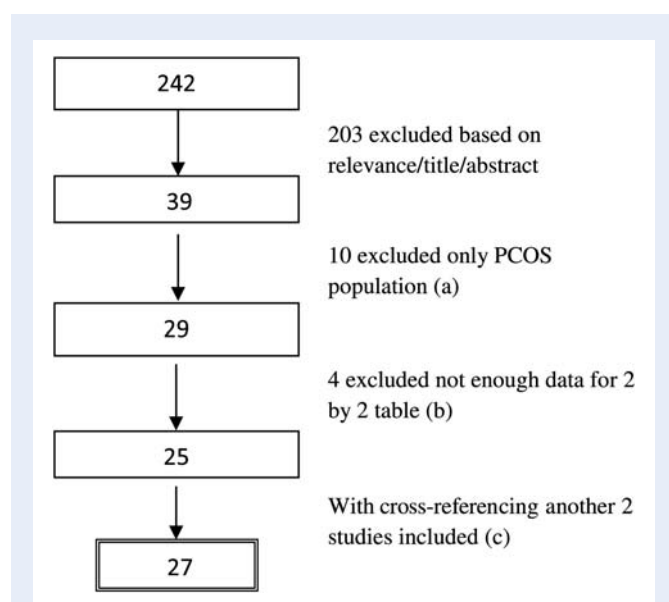


Figure 5 Flowchart in/exclusion studies for outcome ART. (a) Beydoun et al. (2009), McCormick et al. (2008), Eijkemans et al. (2005), Jungheim et al. (2009), Kolibianakis et al. (2003), Li et al. (2010), Liberty et al. (2010), Mulders et al. (2003), Orvieto et al. (2009b), Ozgun et al. (2011), Pagidas et al. (2010). (b). Fadini et al. (2009), Kilic et al. (2009), Kumbak et al. (2010), Kupka et al. (2011). (c). Hill et al. (2011), Sathya et al. (2010).

rates of ART on the other hand. We summarized the current evidence on complications following ART with respect to BMI. We found no impact of overweight or obesity on OHSS, multiple pregnancies or ectopic pregnancies. A slight negative effect on live birth rate is found in overweight and obese women. Literature specifically reporting on the effect of BMI on the aforementioned complications in women with PCOS was lacking.

One of the drawbacks of our review is the lack of publications on complications following ART in general. The articles we found did not study complications of ART in relation to BMI as their primary outcome; as a consequence, not one was powered to show a significant difference. Also with exception of two studies, all were retrospective with the possible selection bias and confounding effect. As our research has been based on this limited and of moderate quality data, the outcome of our study should be put in this perspective. Serious complications like infection, haemorrhage, thromboembolism or even mortality are not documented in relation to BMI. The Safety Interest Group (SIG) Safety and Quality of the ESHRE recommended registering mortality following ART worldwide because of this lack of information. Following this review of the literature, we underscore the importance of achieving better data collection of morbidity following ART.

Furthermore, we were not able to differentiate further between obesity classes because of lacking data. As mentioned earlier, several clinics throughout the world use upper limits for BMI for ART with scarce evidence on morbid obese women as a consequence. One might expect more complications or lower outcome results in obesity class III than in class I (WHO definition obesity class I BMI 30–35 kg/m² and class III BMI > 40 kg/m²) (Luke

et al., 2011). However, in view of the lack of evidence on the outcomes of ART in severe obesity and in view of the little impact that we found from mild obesity, it remains difficult to define a threshold.

We found an OR of 0.90 for the association between overweight and live birth, indicating a 10% reduction in the success rates of IVF in overweight women. The absolute effect of such an association obviously depends on the absolute live birth rates after IVF. When, for example, the probability of live birth is 30% in a normal weight woman, then the success rates of an overweight woman drop to 27.8%. In other words, when we treat 46 normal weight women with IVF, there is one additional pregnancy when compared with when we treat 46 overweight women with the same treatment.

Another drawback is that most articles are retrospective observational cohort studies with the disadvantage of observation bias and confounding. This bias could be overcome with prospective studies where covariate data can be collected extensively and in sufficient detail to more accurately evaluate confounding and effect modification. Moreover, the studies applied different cut-off points to define overweight and obesity, as well as different definitions of outcome and the population of women differed between studies. Because of these differences, we were not able to pool all studies in our analysis, e.g. half of the studies on live birth rate with ~60 000 women could not be used in our analysis (Wittemer et al., 2000; Lintsen et al., 2005; Thum et al., 2007; Matalliotakis et al., 2008; Bellver et al., 2010; Luke et al., 2011) hypothetically changing our conclusion. For argument sake, we therefore performed the analysis including the results of Luke et al., comprising 45 000 ET, to establish the possible impact on our pooled OR. The OR for live birth rate remained within the same margins with OR 0.86 (CI 0.83–0.9) for overweight and OR 0.85 (CI 0.81–0.9) for obese women, now also showing a significant lower live birth rate for obese women.

We expected to find a difference in complication rates in controlled ovarian hyperstimulation due to difficulty monitoring follicles with ultrasound in overweight or obese women. Therefore, we searched literature specifically for this association but we did not identify any study reporting on this subject. As OHSS is found more often in women with PCOS (Tummon et al., 2005), we presumed that there might be a difference between normal and overweight women. However, no literature was found on the subject.

Our results on the effectiveness of ART concur with those of Maheshwari et al. (2007). Since publication of that review, 14 relevant additional studies were published on the subject. We found a moderate negative effect of obesity on ART outcome. Women with a BMI of 25 kg/m² or higher achieve reasonable, but slightly lower live birth rates when compared with normal weight women. The fact that the pooled OR for overweight women is significant, but the pooled OR of obese women lacks statistical significance is probably due to the smaller group of obese women when compared with overweight women, as point estimates for both groups were from the same magnitude. A large study on subfertile women undergoing ART with autologous and donor oocytes subclassifying between several obesity classes did show significant lower live birth rates in increasing obesity classes with autologous oocytes (Luke et al., 2011). However, they compared obesity classes to normal weight women, whereas we tried to find a cut-off value and compare, for example, BMI > 30 kg/m² with BMI < 30 kg/m².

Table II Incidence of positive outcomes after ART in overweight and obese versus normal weight women in the studies analysed.

Author	Design	ART	n	Outcome	Per	Incidence of outcome in overweight ^a versus normal weight women					
						% women		OR (95% CI)	% women		OR (95% CI)
						BMI > 25	BMI < 25		BMI > 30	BMI < 30	
Luke <i>et al.</i> (2011)	Cohort	IVF	451 63	Live birth	ET	34	38	0.9 (0.8 to 0.9)	32	36	0.9 (0.8 to 0.9)
Hill <i>et al.</i> (2011) ^b	Cohort	IVF	117	Live birth	Woman	44	33	1.6 (0.8 to 3.4)	33	40	0.8 (0.3 to 2.1)
Sathya <i>et al.</i> (2010)	Cohort	IVF	308	cp	Woman	41	43	0.9 (0.6 to 1.5)	33	44	0.6 (0.4 to 1.1)
Farhi <i>et al.</i> (2010)	Cohort	IVF	233	Live birth	Woman	41	38	1.1 (0.6 to 2.0)	NA	NA	NA
Kilic <i>et al.</i> (2010)	C-S	IVF	1970	cp	Woman	47	45	1.1 (0.9 to 1.3)	50	44	1.3 (1.1 to 1.5)
Zhang <i>et al.</i> (2010)	Cohort	IVF/ICSI	2628	Live birth	Woman	24	26	0.9 (0.7 to 1.1)	26	26	1.0 (0.4 to 2.4)
Bellver <i>et al.</i> (2010)	Cohort	IVF/ICSI	6500	Live birth	Cycle	28	31	0.9 (0.8 to 1.0)	24	31	0.7 (0.6 to 0.9)
Maheshwari <i>et al.</i> (2009a)	C-S	IVF	1756	Live birth	Woman	23	26	0.9 (0.7 to 1.1)	22	25	0.9 (0.6 to 1.2)
Orvieto <i>et al.</i> (2009a)	Cohort	IVF/ICSI	516	cp	Cycle	NA	NA	NA	20	29	0.6 (0.3 to 1.2)
Mataliotakis <i>et al.</i> (2008)	Cohort	IVF/ICSI	278	Live birth	Woman	47 ^c	46 ^c	1.0 (0.6 to 1.7) ^c	NA	NA	NA
Sneed <i>et al.</i> (2008)	Cohort	IVF/ICSI	1273	Live birth	Woman	21	24	0.8 (0.6 to 1.1)	22	23	0.9 (0.7 to 1.2)
Esinler <i>et al.</i> (2008)	Cohort	ICSI	775	cp	ET	46	45	1.1 (0.8 to 1.4)	48	45	1.2 (0.8 to 1.6)
Martinuzzi <i>et al.</i> (2008)	Cohort	IVF/ICSI	417	op	Woman	45	47	0.9 (0.6 to 1.4)	42	47	0.8 (0.5 to 1.5)
Thum <i>et al.</i> (2007)	Cohort	IVF/ICSI	8145	Live birth	Woman	26 ^d	29 ^d	0.9 (0.8 to 1.0) ^d	24 ^e	29 ^e	0.8 (0.6 to 1.0) ^e
Dokras <i>et al.</i> (2006)	Cohort	IVF/ICSI	1291	Delivery	Woman	42	42	1.0 (0.8 to 1.3)	41	42	0.9 (0.7 to 1.2)
Ku <i>et al.</i> (2006)	Cohort	ICSI	223	cp	Woman	11 ^c	26 ^c	0.3 (0.1 to 1.0) ^c	NA	NA	NA
Dechaud <i>et al.</i> (2006)	Cohort	IVF/ICSI	789	op	Cycle	13	17	0.8 (0.4 to 1.3)	13	16	0.7 (0.3 to 1.8)
Styne-Gross <i>et al.</i> (2005)	Cohort	IVF donor oocyte	536	op	Woman	74	72	1.1 (0.7 to 1.7)	74	73	1.1 (0.6 to 1.9)
Lintsen <i>et al.</i> (2005)	Cohort	IVF	8105	Live birth	Cycle	14	16	0.9 (0.8 to 1.1)	NA	NA	NA
Van Swieten <i>et al.</i> (2005) ^b	Cohort	IVF/ICSI	162	cp	Woman	33	46	0.6 (0.3 to 1.1)	41	41	1.0 (0.5 to 2.3)
Spandorfer <i>et al.</i> (2004)	Cohort	IVF/ICSI	828	cp	Cycle	56 ^f	56 ^f	1.0 (0.7 to 1.5) ^f	NA	NA	NA
Fedorcsak <i>et al.</i> (2004)	Cohort	IVF/ICSI	2660	Live birth	Woman	19	22	0.9 (0.7 to 1.1)	18	21	0.8 (0.6 to 1.1)
Loveland <i>et al.</i> (2001)	Cohort	IVF	139	op	Cycle	25	51	0.3 (0.2 to 0.6)	NA	NA	NA
Salha <i>et al.</i> (2001) ^b	CC	IVF	100	cp	Woman	26 ^d	38 ^d	0.6 (0.2 to 1.3) ^d	NA	NA	NA
Wang <i>et al.</i> (2000)	Cohort	IVF/ICSI	3586	Fecundity	Cycle	40	47	0.8 (0.7 to 0.9)	37	46	0.7 (0.6 to 0.9)
Wittermer <i>et al.</i> (2000)	Cohort	IVF/ICSI	325	Delivery	Cycle	14	17	0.8 (0.4 to 1.7)	NA	NA	NA
Lashen <i>et al.</i> (1999) ^b	CC	IVF	228	cp	Woman	24 ^g	20 ^g	1.2 (0.6 to 2.3) ^g	NA	NA	NA

C-S, cross-sectional; CC, case-control; cp, clinical pregnancy; op, ongoing pregnancy; ET, embryo transfer; NA, not available.

^aComparisons were as stated except where indicated ^cBMI > 24, ^dBMI > 26, ^eBMI > 31, ^fBMI > 27, ^gBMI > 28 versus BMI 20–25.^bProspective trial others were retrospective.

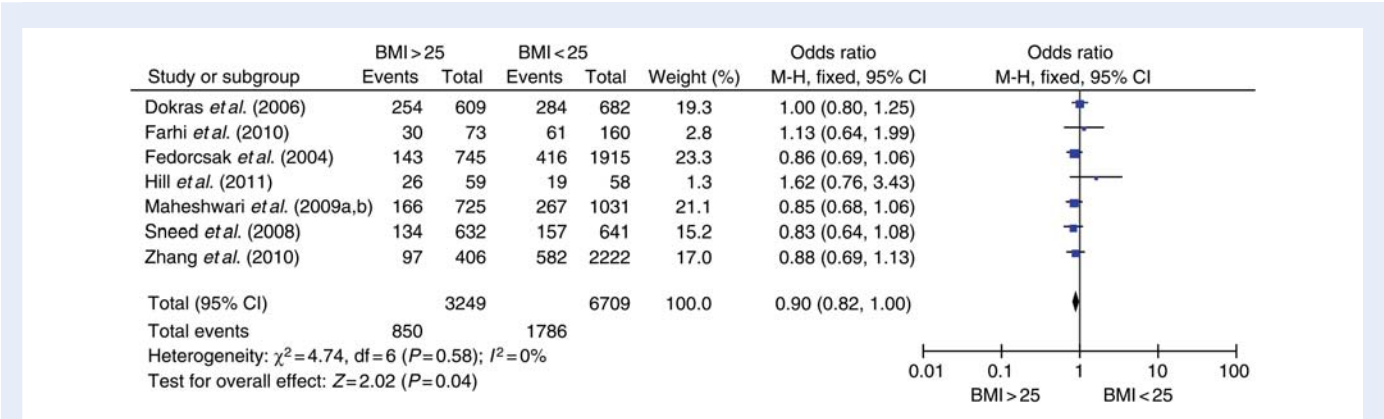


Figure 6 Live birth rate for overweight and normal weight women.

Table III Incidence of positive outcomes after ART in overweight and obese^a compared with normal weight women with PCOS^b

Study	n	Per	Outcome	Incidence (%)		OR (95% CI)	Incidence (%)		OR (95% CI)
				BMI > 25	BMI < 25		BMI > 30	BMI < 30	
Ozgun <i>et al.</i> (2011) ^c	44	Woman	Live birth	NA	NA	NA	22	46	0.3 (0.1 to 1.3)
Orvieto <i>et al.</i> (2009b)	100	Cycle	cp	16	29	0.5 (0.2 to 1.2)	NA	NA	NA
McCormick <i>et al.</i> (2008)	17	Cycle	Live birth	NA	NA	NA	46 ^d	83 ^d	0.2 (0.01 to 1.9) ^d
Kjotrod <i>et al.</i> (2004) ^c	73	Woman	Live birth	NA	NA	NA	38 ^e	39 ^e	0.9 (0.4 to 2.4) ^e

NA, not available; cp, clinical pregnancy.
^aComparisons as stated except where indicated ^dBMI >30 versus BMI 18.5–24.9, ^eBMI > 28.
^bDefined by Rotterdam criteria.
^cProspective study others are retrospective.

In the debate whether overweight or obese women should be denied access to ART, it is of interest to compare the effect of BMI with that of female age on ART outcome, as this is a well-accepted criterion to deny or allow ART (Templeton *et al.*, 1996). In view of the decreasing success rates of ART in older women, most countries have an upper limit for age with respect to access to ART programmes. In the Netherlands, national guidelines recommend not offering ART to women older than 41 years because of poor pregnancy chances; but in clinical practice, this threshold has moved to an age of 43.

Figure 7 shows live birth rates following IVF in relation to female age for women with a BMI of <25 and >25 kg/m², which decrease from 26% for younger women to 10% for women aged 40 (Mareshwari *et al.*, 2009b). When we consider an effect of overweight and obesity as pooled OR 0.9, the profound effect of age is much stronger when compared with the moderate effect of overweight on the live birth rate following IVF. This combined OR 0.9 should be viewed in the light of the earlier mentioned remarks on the level of evidence of the included studies.

Although high BMI is associated with obstetric and perinatal complications, the BMI thresholds now applied in some countries are not justified by empirical evidence. Since weight loss programmes have shown limited success, thus indicating how difficult it is to lose

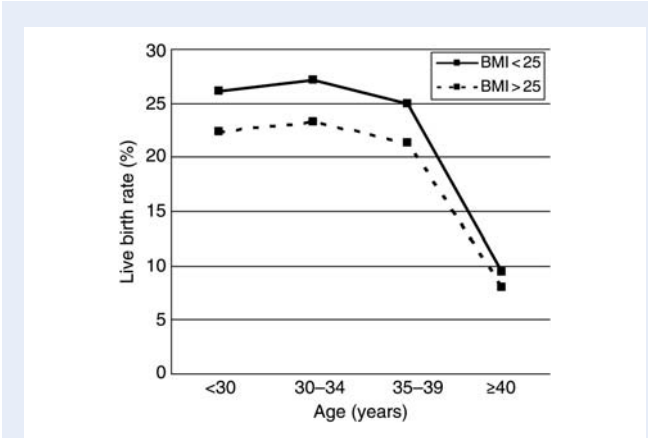


Figure 7 Live birth rates following IVF for overweight and normal weight women in different age groups.

weight, certainly in older patients, the gain in outcome variables must be balanced against the detrimental effect of older age (Sneed *et al.*, 2008). Indeed, to delay attempts to conceive to the age of 40 is probably more detrimental and perhaps more changeable than the decision to gain weight.

In the Netherlands, at present, a multicentre randomized controlled trial is in process which compares lifestyle intervention prior to conventional fertility care (including ART) with direct conventional fertility care in women with a BMI of ≥ 29 kg/m² (Mutsaerts et al., 2010). If this study shows better results in the treatment group, this would provide scientific evidence for recommending lifestyle intervention before fertility treatment is started.

Apart from the slightly negative effect of BMI ≥ 25 kg/m² on ART outcome, there is a substantial risk of pregnancy complications in overweight and obese women, such as hypertension, gestational diabetes, macrosomia and an increased risk of Caesarean section and perinatal death (Garbaciak et al., 1985; Edwards et al., 1996; Weiss et al., 2004). Moreover, the general health risk in terms of increased prevalence of, for example, cardiovascular disease and type 2 diabetes of overweight is well described (Visscher and Seidell, 2001). In our opinion, overweight women should be informed about these overall health risks, obstetric risks and slightly lower success rates of ART when seeking fertility care.

In conclusion, there is a lack of studies reporting on complications following ART. In the published literature, we did not find more complications in subfertile overweight and obese women when compared with subfertile normal weight women. We found slightly lower success rates in these overweight women following ART. Therefore, we feel there is no evidence for excluding women above a certain BMI threshold from ART but counselling on the increased obstetrical risks is mandatory. Furthermore, following the recommendations of the SIG Safety and Quality of the ESHRE, an international complication registration system for ART should be implemented to increase safety of women undergoing ART.

Authors' roles

A.M.H.K. contributed to the study design, conception, data acquisition, analysis and writing of the manuscript. M.A.Q.M. performed statistical analyses, contributed to data acquisition, revising and approval of the final draft. W.K.H.K. and F.J.B. took part in revising and approval of the final draft. J.A.L. contributed to the design, took part in revising and approval of the final draft. B.W.M. and A.H. contributed to the design, conception, drafting, revising and approval of the final draft.

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Conflict of interest

None declared.

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